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Syringomatous Structures in Extramammary Paget Disease: A Potential Diagnostic Pitfall

Anastasia M. Konstantinova, MD, PhD,† Malcolm M. Hayes, MB, MMed (Anat Path), FRCPath,‡ Colin J. R. Stewart, FRCPA,§ Jose A. Plaza, MD,¶ Michal Michal, MD,‖** Katrin Kerl, MD,†† and Dmitry V. Kazakov, MD, PhD**††*

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Key Words: extramammary Paget disease, syringoma, syringoma-like structures, vulva

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INTRODUCTION

Primary extramammary Paget disease (EMPD) is a form of intraepithelial adenocarcinoma of uncertain histogenesis. Various origins have been proposed including apocrine glands, eccrine glands, hair follicles,[1–8] anogenital mammary-like glands, Toker cells, or pluripotential stem cells in the epidermis.[9–14] Unlike mammary Paget disease, EMPD is seldom associated with an underlying ductal carcinoma in situ or invasive carcinoma except for those cases that arise within an anogenital mammary-like glands.[15–18] In contrast, syringoma is a benign adnexal neoplasm occurring in the superficial dermis.[19] Both lesions occur on the vulva and perineal skin but, there is no known relationship between them. In the vulva, syringomas are often associated with chronic pruritis, also a common symptom of EMPD.[20,21]

During histopathological examination of vulvectomy specimens from 10 patients with EMPD we encountered small syringoma-like foci in the dermis beneath the involved epidermis and occasionally beyond the margin of the EMPD. Our study is focused on these unusual glandular structures, which could be interpreted as invasive carcinoma and therefore represent a diagnostic pitfall for pathologists unaware of their existence.

MATERIALS AND METHODS

The 10 patients constituting the subject of this report were found among 98 cases of EMPD in the joint consultation and institutional files of the authors. Clinical information was obtained from the patients' physicians and from review of case records. Each case was stained with hematoxylin and eosin and mucicarmine, and immunohistochemical staining for CK7 and p63 was performed on 9 blocks from 7 patients.

In 3 cases, syringomatous change was seen both in the initial biopsy and in subsequent specimens demonstrating local recurrence of the EMPD. A total of 13 specimens were examined comprising 10 vulvectomies with the number of tissue blocks ranging from 14 to 27, and 3 wide local excisions sampled in 4, 13, and 18 blocks, respectively. Overall, syringomatous structures were recognized in 31 of 247 blocks studied (Table 1).

CLINICAL DATA

All patients were women whose ages ranged from 49 to 93 years. Eight patients presented with a newly diagnosed EMPD, whereas the other 2 had a previous history of EMPD treated by various modalities (Table 1). All patients clinically manifested flat or slightly elevated erythematous or white-gray areas, with some scaling, excoriations, and crust consistent with primary EMPD (Fig. 1). In 1 patient, small papules were present within and outside the affected areas, but these proved to be infundibular cysts on histology. None of the patients had had a history of a carcinoma in the urogenital or gastrointestinal tract that might have suggested secondary skin involvement from these sites. One patient had a history of vulvar squamous cell carcinoma.

From the *Department of Pathology, Clinical Research and Practical Center for Specialized Oncological Care, Saint Petersburg, Russia; †Department of Pathology, Medical Faculty, Saint–Petersburg State University, Saint Petersburg, Russia; ‡Department of Pathology, BC Cancer Agency, Vancouver, British Columbia, Canada; §Department of Histopathology, King Edward Memorial Hospital, Perth, Australia; ¶Department of Pathology, Division of Dermatopathology, Medical College of Wisconsin, Milwaukee, WI; ‖Sikl's Department of Pathology, Bioptical Laboratory, Pilsen, Czech Republic; **Sikl's Department of Pathology, Medical Faculty in Pilsen, Charles University in Prague, Pilsen, Czech Republic; and ††Department of Dermatology, University Hospital Zurich, Zurich, Switzerland.

The authors declare no conflicts of interest.

Reprints: Dmitry V. Kazakov, MD, PhD, Sikl's Department of Pathology, Charles University Medical Faculty Hospital, Alej Svobody 80, 304 60 Pilsen, Czech Republic (e-mail: kazakov@medima.cz).

TABLE 1. Main Clinical Features of the Patients

Case No	Sex/Age	Clinical Data and Follow-up	Tissue Blocks*	Location of Syringomatous Structures
1	F/75	NED at 57 mo	2/17	Beneath AA (×2)
2	F/75	Recurrence treated with second excision at 20 mo and second recurrence with invasive adenocarcinoma at 101 mo	3/27	Beneath AA (×1)
				Outside AA (×2)
			6/23	Beneath AA (×5)
				Outside AA (×1)
3	F/60	NED at 34 mo	1/25	Beneath AA (×1)
4	F/80	Four recurrences in next 74 mo. Further treatment refused	1/19	Beneath AA (×1)
			2/23	Beneath AA (×2)
5	F/84	Wide local excision (up to 70 × 18 mm in size). Recurrence in 3 yrs and diagnosis of breast carcinoma at the same time. No further treatment for EMPD (refused by patient). DUC 5 yrs later	1/18	Beneath AA (×1)
			1/21	Beneath AA (×1)
6	F/81	One-year history of EMPD treated with wide local excision. NED at 60 mo	1/4	Beneath AA (×1)
7	F/93	Previous resection of squamous cell carcinoma of the vulva. Review at 2 mo, probable residual EMPD. Patient refused further treatment. DUC at 13 mo	1/17	Beneath AA (×1) Pagetoid spread along syringomatous structures
8	F/49	NED at 62 mo	8/14	Multifocal in 3 blocks all beneath AA (×8)
9	F/74	NED at 60 mo	1/20	Beneath AA (×1)
10	F/65	Wide local excision (70 × 32 mm in size). AWD (metastases to supraclavicular and inguinal lymph nodes)	3/13	Beneath AA (×3)

NED no evidence of disease.
AWD alive with disease.
DUC death of unknown (case 5) or unrelated (case 7) cause.
AA areas affected by the EMPD.
*The first number indicates the number of tissue blocks in which the syringomatous structures were identified. The number after slash indicates the total number of blocks available from case.

MICROSCOPIC FEATURES

The typical microscopic features of EMPD were present in all cases. These included an intraepithelial spread of cells with ample cytoplasm distributed singly and in small clusters. In all cases, small gland-like elements formed by the neoplastic cells were identified within the epidermis. In 2 cases, malignant glandular elements were seen lying free in the upper dermis consistent with microinvasion. Apart from these neoplastic glandular elements, all cases showed benign-looking dermal ductal structures resembling classical syringoma (Fig. 2). These syringomatous foci were present both beneath the areas affected by the EMPD and outside them, sometimes being noted in sections taken from the margins of excision. The syringomatous structures appeared as a cluster of benign looking ductal elements with attenuated epithelium, including focal tadpole-like appearances. Their connection to an eccrine secretory unit could be traced on serial sections (Fig. 3). In 1 case, syringomatous ducts were embedded within a dense sclerotic stroma imparting the appearance of an authentic incipient syringoma. This case also showed multifocal (2–3 foci) syringomatous lesions. In 1 case, syringomatous structures were colonized by the neoplastic cells from the EMPD (Fig. 4).

On immuhistochemical staining, syringoma-like structures were identified in 6 blocks from 4 patients. Staining for p63 highlighted the preserved native cells in the basal layer of the epidermis and in syringoma-like structures (Fig. 5A). Staining for CK7 revealed neoplastic cells, although the syringoma-like structures were negative (Fig. 5B).

DISCUSSION

Although glandular and pseudoglandular formations are well known features of EMPD, syringomatous structures in this condition have seldom been mentioned in the literature. Requena et al[22] in their monograph on apocrine tumors of the skin in figure 38.10 document glandular elements naming them syringomatous structures. However, to our eyes, those glandular elements more likely represent neoplastic glands with an attenuated epithelial lining rather than a benign syringomatous lesion. The syringomatous structures we describe are different. Most seem to represent hyperplasia (and dilatation) of preexisting eccrine ducts, as these were clustered, and a connection to eccrine secretory lobules could be followed on serial sections. In 1 case, the syringomatous

FIGURE 1. Clinical appearance of EMPD: Erythematous erosive areas (A, case 8. B, case 3). Note small papules within the affected area and on normal skin (B). Histopathologically these represented infundibular cysts.

glands were embedded within a dense sclerotic stroma and the appearance was highly reminiscent of a small syringoma. Similar syringoma-like ductal proliferations are rarely found in different types of alopecia, especially scarring alopecia, but these are usually very small, focal, and are devoid of the typical sclerotic stroma that characterizes true syringoma. Although initially believed to represent true syringomas causing alopecia, these ductal proliferations were later presumed to be a reactive process secondary to the surrounding inflammation and dermal fibrosis.[23–27] It has been suggested that these ductal proliferations are the result of destruction of the acrosyringium by lymphoid infiltration ("autoimmune acrosyringitis") resulting in loss of structural continuity of the acrosyringium followed by secondary proliferation of the disrupted ducts.[28] Other inflammatory and neoplastic conditions in which syringomatous ductal proliferations have been reported include Grover disease, leukemia cutis, prior irradiation, reexcision specimens, and prurigo nodularis.[29–32] We presume that persistent rubbing, excoriation, and blockage of the intraepidermal acrosyringia by the EMPD may all contribute to the disruption and secondary hyperplasia/dilatation of eccrine ducts to form syringomatous structures.

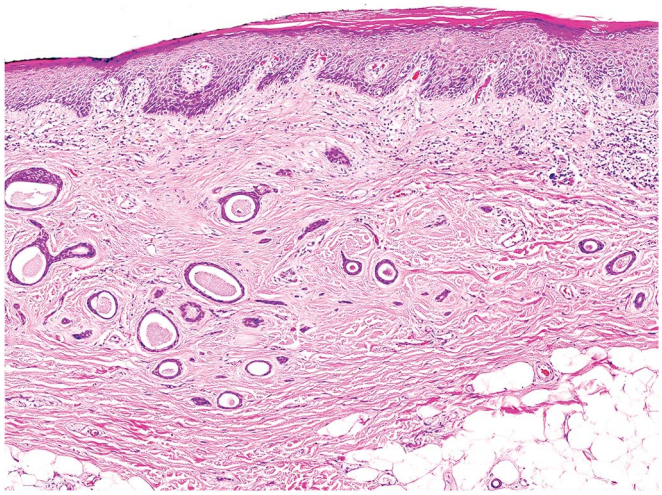

FIGURE 2. Syringoma-like structures in EMPD: Small ductal structures lined by bland-looking epithelial cells. Note tadpole-like appearances and sclerotic stroma reminiscent of syringoma. Intraepidermal carcinoma cells are evident above the lesion.

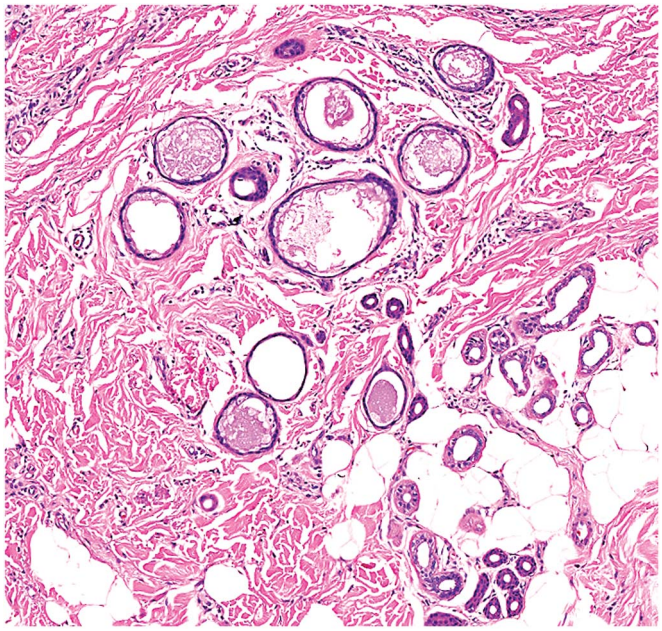

FIGURE 3. Connection of syringomatous structures to an eccrine secretory unit suggests that these may represent hyperplastic and dilated eccrine ducts.

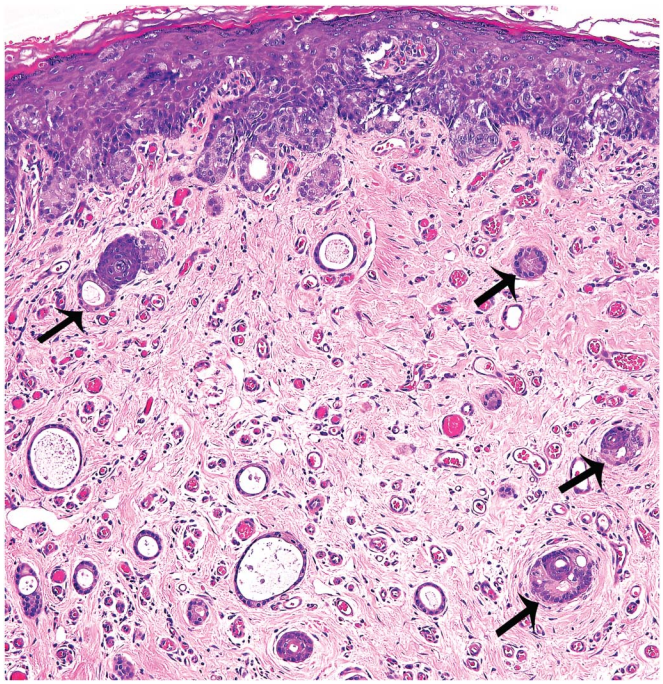

FIGURE 4. Involvement of syringomatous structures by neoplastic cells (arrows).

Whatever their pathogenesis, the syringomatous structures in EMPD represent a diagnostic pitfall, which is actually 2-fold. First, they should not be mistaken for true invasive neoplastic glandular elements. However, as demonstrated by our case 7, these syringomatous glands may themselves be colonized by the neoplastic cells from the EMPD and perhaps serve as a conduit for the malignant cells to spread into the deeper regions of the dermis. Adnexotropism of neoplastic cells in EMPD is well known.[10] In some cases of EMPD, we observed foci in which the neoplastic cells invaded the stroma from involved adnexal structures (hair follicles, apocrine, and eccrine glands) deep in the dermis. This pattern contrasts with the type of microinvasion defined by Feuer et al[33] who described invasion by the neoplastic elements to a depth of no more than 1 mm below the basement membrane of the surface epithelium. Such invasion from involved adnexal structures is similar to the pattern seen in carcinoma of the cervix, where microinvasion from involved endocervical glands is not uncommon.

The spectrum of EMPD includes cytologic variations in the neoplastic cells, single cell distribution and nested patterns, proliferative epidermal lesions, syringocystadenocarcinoma papilliferum in situ like areas, and hyperpigmented forms, rarely with melanocytic hyperplasia.[16,21] A single case of EMPD with oncocytic changes has been described.[34] The syringoma-like structures reported here extend the morphological spectrum

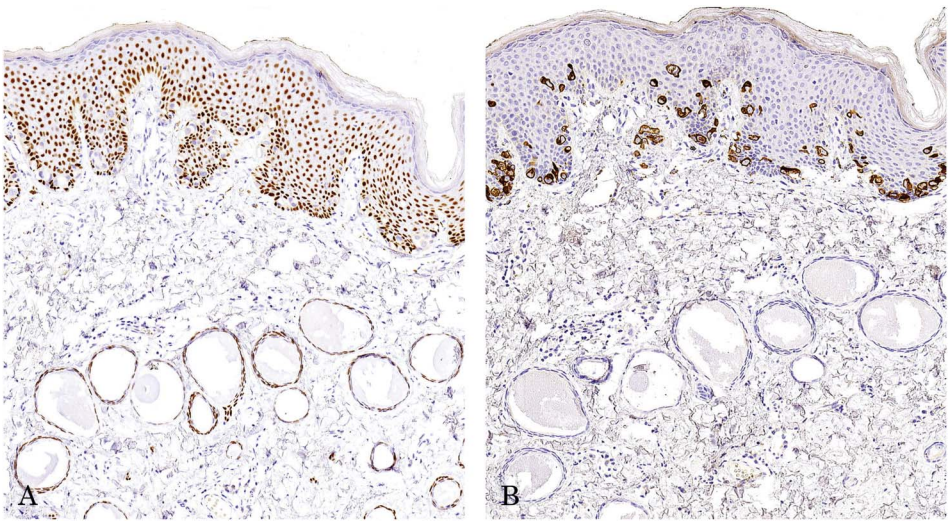

FIGURE 5. p63 and CK7 immunostaining of syringoma-like structures in EMPD. A, Staining for p63 highlights the preserved native cells in the basal layer of the epidermis and in syringoma-like structures. B, Staining for CK7 reveals neoplastic cells while syringoma-like structures are negative.

of EMPD, and awareness of these structures is important to avoid their misinterpretation as an invasive component of the carcinoma.

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